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Amandine E. Bonnet, Yannick Marchalant

Aging and Disease
www.aginganddisease.org
Volume 6, Number 5; 400-405, October 2015
http://dx.doi.org/10.14336/AD.2015.0617

Review Article

Potential Therapeutical Contributions of the Endocannabinoid System towards Aging and Alzheimer's Disease

Amandine E. Bonnet[1], Yannick Marchalant[2*]

[1]CNRS, NICN UMR 7259 Aix-Marseille University, 13344 Marseille, France.
[2]Department of Psychology/Neuroscience program, Central Michigan University, MI 48859, USA

[Received June 1, 2015; Revised June 17, 2015; Accepted June 17, 2015]

ABSTRACT: Aging can lead to decline in cognition, notably due to neurodegenerative processes overwhelming the brain over time. As people live longer, numerous concerns are rightfully raised toward long-term slowly incapacitating diseases with no cure, such as Alzheimer's disease. Since the early 2000's, the role of neuroinflammation has been scrutinized for its potential role in the development of diverse neurodegenerative diseases notably because of its slow onset and chronic nature in aging. Despite the lack of success yet, treatment of chronic neuroinflammation could help alleviate process implicated in neurodegenerative disease. A growing number of studies including our own have aimed at the endocannabinoid system and unfolded unique effects of this system on neuroinflammation, neurogenesis and hallmarks of Alzheimer's disease and made it a reasonable target in the context of normal and pathological brain aging.

Key words: Cannabinoids, Neuroinflammation, Neurogenesis, Aging, Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and accounts for the majority of diagnosed dementia after age 60. It is estimated to currently affect between 20 and 30 million people worldwide with an incidence of the disease between 3 and 30% over the age of 60 [1]. As life expectancy increases, the prevalence of AD and its burden on healthcare is very likely to increase dramatically in the next few decades. Currently available drugs do not reverse or stop the progression of the disease, but only relieve certain cognitive symptoms and thus provide no cure for this growing health and economic concern.

Alzheimer's disease

The disease is characterized by a slow but progressive loss of cognitive functions associated with neurodegeneration, as well as an important neuroinflammation [2]. More classically, AD is described mainly by two post-mortem histological diagnostic features that are extracellular amyloid β protein (Aβ) deposition and Tau hyperphosphorylation forming intracellular neurofibrillary tangles (NFT) [3–5]. Mutations in the genes coding for amyloid precursor protein (*APP*), presenilin-1 or -2 (*PSEN1*, *PSEN2)* have been identified as implicated in familial forms of AD and are known to favour the production of different Aβ oligomeric assemblies and amyloid plaques in various region of the brain, notably the hippocampus, cortex and amygdala. This broadly accepted hypothesis, known as the amyloid cascade, states that the cause of AD pathophysiology is the massive production of Aβ following cleavage of the APP by β-secretase and γ-secretase complex successively [6]. It also implies that all other hallmarks (inflammation and Tau hyperphosphorylation notably) are direct consequences of Aβ exacerbated production. Nonetheless

***Correspondence should be addressed to:** Yannick Marchalant, Ph.D., Central Michigan University, Health Profession Building, HP 2181, 48859 Mount Pleasant, MI, USA. Email: march1y@cmich.edu
ISSN: 2152-5250

Tau proteins when hyperphosphorylated can form NFT that in turn impair intra-neuronal communication [7] and lead directly to cell death [5]. Although the amyloid cascade hypothesis is strongly supported, particularly in the familial forms of the disease that account for less than 5 per cent of all cases, increasing evidence suggests that the evolution/causes of the sporadic forms of the disease are different from the familial ones [8].

Indeed, another important feature of AD's pathology is the presence of a chronic inflammatory component. Several reviews over the last decade have extensively summarized those events [2,9]. If inflammatory processes are well known to accompany tissue damage in many neurodegenerative diseases as Parkinson's [10] or amyotrophic lateral sclerosis [11], AD's progression seems to be tightly linked to chronic inflammation. In fact, strong epidemiological evidence suggests inflammatory processes as partly responsible for the development of AD. For example, long-term use of non-steroidal anti-inflammatory drugs (NSAID) lowers the prevalence of AD by 30-60% [12–14]. Furthermore, biochemical analysis of AD brains revealed elevated levels of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α or S100β [2,15]. On an histological point of view, gliosis (astrocytosis as well as microgliosis) is prominent and most plaques are surrounded by activated astrocytes and/or invaded by activated microglia [16,17]. A lot of the studies have focused on microglial cells, but it is now clear that microglial cells are assisted by astrocytes and endothelial cells [18] to maintain a chronic inflammatory state of the brain. This long lasting process (probably established over decades in the human brain) induces a chronic "stress" on neurons and affects their normal range of functioning. It has been clearly established that cell cycle proteins are activated [19], reactive oxygen species produced [19], mitochondrial function reduced [21] and denditric/axonal transport impaired [20].

Although numerous studies have validated inflammatory mediators or the brain's immune system in AD, the precise role of inflammatory processes in the disease pathophysiology is still highly controversial (from beneficial to possibly triggering AD [21,22]. As mentioned above, McGeer and coll. provided first support for a key role of inflammation in AD through a meta-analysis of 17 epidemiological studies, indicating that NSAIDs might decrease the risk of AD [12]. This has been followed by other epidemiological studies reporting that elevated levels of inflammatory factors (such as IL-6 and C-reactive protein notably) could be found in the plasma of AD patients long before clinical onset of the disease [23,24]. Moreover, diagnosis of dementia was more likely to be done during infection episodes [25]. Following such evidence, clinical trials however failed to show a beneficial effect of anti-inflammatory drugs in patients with symptomatic AD or mild cognitive impairment [26,27]. Based on the assumption that treatment needed to be timely, extended treatment of asymptomatic individuals with naproxen reduced the incidence of AD, supporting a benefit when NSAIDs are administered in early asymptomatic phases of the disease [28]. Moreover, some patients with high plaque burden exhibit no dementia [29] and also demonstrate almost no evidence of neuroinflammation or neurodegeneration [30]. This actually is in accordance with observations made in several transgenic mouse models of AD often devoid of strong neuroinflammatory response or neurodegeneration [31]. Finally, studies using non-invasive brain imaging (MRI or PET) revealed that decrease in cognition performance in patients with AD is rather correlated with increased microglial activation, than with Aβ load [32,33].

On a cellular point of view, microglia is commonly accepted as recruited to clear Aβ aggregates even if ablation of microglia in an AD mouse model wasn't found to change disease progression [34,35]. On the other end, microglia might also be primarily recruited to clear debris from neurons and neurites within plaques [36], Aβ aggregates included in the process. Finally, aged microglia may become senescent and its response non-appropriate in normal/pathological conditions [37], potentially explaining the role of inflammation early in the pathogenesis of AD. In particular, its hyper-active state and sustained secretion of pro-inflammatory elements may lead to inefficient clearance of degenerating cells, leading to an overall toxic microenvironment prone to further degeneration and aggregate of proteins in the extracellular space.

Overall, it seems clear that neuroinflammation plays an important role in AD and that it may even influence disease progression very early on, especially as AD is diagnosed rather late while the mechanisms leading to neurodegeneration are already in motion probably decades before. To support this assumption, recent work from Knuesel's laboratory showed that chronic inflammation caused by viral infection with PolyI:C during the foetal period of non-transgenic animals can lead to very early changes in APP cleavage suggesting that neuroinflammation could trigger AD-like pathology in those animals [38].

Cannabinoids

The field of cannabinoid research has flourished over the past decades and have brought to light numerous functions of this system in normal and pathological conditions. So far two types of cannabinoid receptors have been identified, CB1 and CB2 [39,40]. Nonetheless other receptors are responsive to cannabinoids compounds: transient receptor potential vannilloid-1 (TRPV1),

peroxisome proliferator-activated receptors α and β (PPARα, PPARβ, see [41] for review). Discovery of cannabinoid receptors (CBr) lead to the finding of endogenous agonists for these receptors called endocannabinoids (EC). In the central nervous system (CNS), CB1 is overwhelmingly represented over CB2, and the most abundant G protein-coupled receptors in the brain. CB1 is found in neurons and glial cells and particularly abundant in cortical regions, the hippocampus, cerebellum and basal ganglia [42]. It regulates numerous cerebral functions ranging from pain perception, motor control and feeding to emotion and memory processes. CB2 on the other end may be restricted to microglia [43] or neurons in the brainstem [44] and cerebellum [45]. Endocannabinoids are mostly derived from arachidonic acid, arachidonoylethanolamide (anandamide), and 2-arachidonoyl glycerol (2-AG), synthesized on-demand post-synaptically and released following calcium influx [46]. These EC in combination with the two known CBr constitute the endocannabinoid system (ECS). Deactivation of EC is rapid and due to enzymatic degradation in the synaptic cleft or reuptake [47]. The ECS is thought to be a neuromodulator [48] and an immunomodulator [49]. Cannabinoids demonstrated neuroprotective properties in numerous experimental conditions, some been or currently evaluated in various diseases ranging from cancer to AIDS for their peripheral analgesic and immunosuppressive properties [50,51]. Moreover, their anti-inflammatory properties could prove beneficial in the treatment of multiple sclerosis, Parkinson's disease and AD [52–57].

Cannabinoids and Alzheimer's disease

A growing amount of evidence points out to the possible implication of the ECS in the regulation of events occurring during the course of AD progression, particularly on the regulation of amyloid clearance and inflammation. *Post-mortem* analysis of AD brains demonstrated changes in the expression of CB1 but those remains still unclear. Some authors witnesses reduction of CB1 expression in cortical areas [58,59], a finding that is similar to that seen in aged rats [54], while others demonstrated no changes in the cortex or hippocampus of AD patients [60–63]. Moreover, CB1 levels do not correlates with AD markers or cognitive status [59]. On the other hand, CB2 increase has been clearly identified, notably located on microglia within the amyloid rich plaques [58,59] and Solas and coll. correlated level of CB2 receptors with Aβ42 level and plaques [59]. Moreover, up-regulation of the fatty acid amide hydrolase occurs within plaques and might be responsible for increase in metabolites from anandamide degradation, such as arachidonic acid, and thus contribute to the inflammatory process seen in AD [60].

Several reports over the last two decades demonstrate the potential benefits from the modulation of the ECS over amyloid β and Tau hyper-phosphorylation. *In vitro* studies demonstrated benefits of the use of different EC on cell survival following Aβ exposition [64–67] and on Tau hyper-phosphorylation [68]. Morevover, Aβ infusion *in vivo* (in rats and mice) is associated with gliosis and memory impairment, effects that can be reversed by diverse CB1, CB2 or mixed activation [58,69–73]. Two groups in Spain (De Ceballos and Ferrer's laboratories) have also demonstrated the cognitive benefits of chronic infusion of EC in transgenic mice model of AD [74–76]. Ferrer's group in particular also showed that chronic infusion of a CB1 or CB2 agonist could decrease Tau hyper-phosphorylation in APP/PS1 mice model of AD [74,75]. Nonetheless, most studies looking at the modulation of neuroinflammation using cannabinoids have mainly focused on CB2 receptors as they are mostly expressed on microglial cells. Studies mentioned earlier [58,68,69,71] have observed reduction in microglial activation and pro-inflammatory cytokines following infusion of Aβ in rodents. But as in many studies on AD rodent models, those studies have difficulty pointing out if CB2 modulation benefits come from the reduction of neuroinflammatory processes *per se* or by the reduction of Aβ activation of the neuroinflammatory system. Our lab did provide some potential clues on the role of the different CB receptors in this context. Indeed, our work demonstrated the anti-inflammatory potential using WIN-55,212-2 chronically on chronic neuroinflammation in young and aged rats [54,56,77] as well the neurogenic and cognitive effect of WIN-55,212-2 in aged animals [55]. Our data suggested that the anti-inflammmatory effect of WIN-55,212-2 could be due to its activity on TRPV1 receptors and its neurogenic effects linked to both CB1 and CB2 receptor.

Conclusion

Because of the complexity of pathological mechanisms involved in AD progression, a multi-drug approach seems to emerge as a better potential alternative as none of the available drug therapies are capable of altering the progression of the disease. The pleiotropic effects of cannabinoids, the numerous specific pharmacological tools to target its receptors and the growing number of pre-clinical effects on AD rodent models should finally raise the interest of the research community and be seen as a valuable alternative to slow disease progression or reduce some of the cognitive symptoms in AD.

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